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Editorial

Does the timing of acute rejection matter with the graft outcome in kidney transplantation?

Acute rejection (AR) is a major complication of kidney transplantation (KT). Although advances in immunosuppressive therapy have reduced the incidence of AR, the effect of AR on allograft dysfunction remains an important issue. The number of AR episodes, their severity and type, patient responses to the treatment, and the timing of AR are all potential determinants of graft outcomes [1,2]. Of special interest to many researchers is the role of timing of AR episodes, and what effects timing has on graft outcomes. The primary reason for this interest is that the physiological environment of the allograft changes gradually with time. After KT, dosing of immunosuppressive therapy decreases over time, and graft function gradually declines because of immunologic damage, infection, aging, and chronic exposure to calcineurin inhibitors. Additionally, immune responses to the allograft might be mediated by different mechanisms related to how much time has passed after transplantation [3,4].

In this issue of *Kidney Research and Clinical Practice*, Koo et al [5] investigated the impact of time of AR on long-term graft survival in a single-center cohort. They enrolled 709 patients who had undergone KT between 2000 and 2009 and found that both early- and late-onset AR significantly influences graft outcomes.

Previously, several studies examined the influence of timing of AR on graft outcomes. In 2003, Sijpkens et al [4] found that AR occurring more than 3 months after KT was associated with poorer graft outcomes than AR that occurred during the first 3 months. Interestingly, they also found that human leukocyte antigen (HLA) Class I mismatches predicted late AR, whereas HLA Class II mismatches were associated with early AR. This suggests that direct and indirect pathways of allorecognition may play a role in the pathophysiology of early and late AR, respectively. In 2008, Opelz and Dohler [6] found that late AR is more severe than early AR, as reflected by incomplete functional recovery. Late AR was more difficult to reverse by rejection treatment than early AR and therefore led to poorer long-term outcomes. Most recently, Krisl et al [7] examined how the type of AR, in addition to timing, affects graft outcomes. The authors found that late-onset antibody-mediated rejection was associated with significantly worse graft survival compared with other types and timing of AR, suggesting an important role of humoral immunity in graft outcomes.

Despite these results, it is difficult to conclude that the timing of AR is a critical factor determining graft outcomes. Recent immunosuppressive strategies using tacrolimus and mycophenolate mofetil have contributed to improvement of graft outcomes [8,9]; earlier studies, however, included many patients taking cyclosporine with azathioprine. Therefore, the results are not sufficiently informative about the effects of AR in the current era of immunosuppression. Additionally, 70–100% of donors in previous studies were deceased donors. However, living donors account for a large proportion of the donor population in Asian countries. In Korea, more than 50% of KTs use kidneys from living donors [10]. Different donor characteristics can lead to varied immunologic environments and thus influence the effect of AR on graft outcomes. In addition, we should consider the role of relatively short cold ischemic times in Korea because cold ischemia enhances the immune response to an allograft and affects clinical features of AR. Consequently, the impact of early and late AR on graft survival in Korea needs to be investigated using regional data.

In the present study, Koo et al [5] examined these issues with a cohort of recent KT patients in a single center. They found that there were no significant differences in graft survival according to the timing of AR, although both early and late AR had negative effects on outcomes compared with no AR. As a result, they conclude that both early and late AR present major barriers to improving long-term graft survival. Additionally, male sex and HLA mismatch were risk factors for early AR, whereas younger age of recipient and high panel-reactive antibody levels predicted late AR. However, this study has limitations in the analysis of the factors that may have affected the results, such as baseline renal function at rejection, AR severity, AR consequences, viral infections, *de novo* renal disease, and histological findings of microcirculatory inflammation and chronic changes.

The major conclusion of this study is that compared with nonimmunologic factors, AR was the most significant risk factor associated with poor graft survival. To improve graft survival, we should aim to reduce the number of AR episodes and their severity and enhance responses to treatment

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regardless of the timing of AR onset. In particular, an important issue raised by this study was whether early AR is a significant risk factor for graft failure, and the authors showed the importance of early AR in graft survival. Besides, antibody-associated graft injury needs to be considered a major risk factor of late-onset AR because high panel-reactive antibody was associated with late AR. Although there is a lack of precise data about the type of AR, implementing steps such as immunologic monitoring, early detection, and treatment of humoral immune response should be critical for improving prognosis. Finally, this study is valuable because the authors examined the influence of AR timing on graft survival in patients receiving the current standards of immunosuppressive therapy. We are encouraged by the recent establishment of the national database, Korean Organ Transplant Registry [10]. Comparable with the Scientific Registry of Transplant Recipient, the Collaborative Transplant Study, and the Australia and New Zealand Dialysis and Transplant Registry in other countries, we have our own transplantation database system that will be used for large-scale researches. The Korean Organ Transplant Registry data will be of help to more clearly define the impact of AR and related clinical features on patient outcomes.

Conflicts of interest

The author has no conflicts of interest to declare.

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